

## *HIV This Week*: what scientific journals said

Welcome to the fifty-sixth issue of *HIV This Week*! In this issue we cover **basic science** (a real puzzler: how could not having DARC, a red blood cell receptor, increase risk of HIV infection while slowing HIV disease progression?; viral tropism affects CD4 cell counts and clinical progression but not response to the first treatment regimen), **HIV testing** (radio role models influence pregnant women in Botswana; low interest and uptake of HIV testing in rural Tanzania), **sexual transmission** (receptive anal intercourse higher than many assume in African HIV prevention trial settings), **antiretroviral treatment** (rolling out the public health approach in Africa, Asia, and South America; more frequent CD4 count monitoring before treatment starts can save many more life years), **post-exposure prophylaxis** (one third of rape survivors who start prophylaxis in Ontario finish the 28-day course), **trial design and conduct** (community advisory boards in Peru, Zimbabwe, and Thailand demonstrate their value; vaccine trial site preparation: what is the Hawthorne effect anyway?; selecting futility stopping thresholds in clinical trials), **cardiovascular disease and HIV** (3 mechanisms may explain the risk of cardiovascular disease in people living with HIV; Brazilian children and adolescents with HIV need cardiovascular prevention programmes), **molecular epidemiology** (a window on the dynamics of the Bangladesh HIV epidemic), **spirituality** (Karmic healing in Thailand; secular, spiritual, and religious prayer among people living with HIV in the United Kingdom), **hepatitis** (much more to learn about co-infections in Africa), **young people** (13 years pass and not much changes among school children in Northern Tanzania), and **malaria** (placental malaria increases mother-to-child HIV, irrespective of viral load).

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### 1. *Basic science*

Weijing He, Stuart Neil, Hemant Kulkarni, Edward Wright, Brian K. Agan, Vincent C. Marconi, Matthew J. Dolan, Robin A. Weiss, and Sunil K. Ahuja. Duffy Antigen Receptor for Chemokines

**Mediates trans-Infection of HIV-1 from Red Blood Cells to Target Cells and Affects HIV-AIDS Susceptibility. *Cell Host & Microbe*. 2008;4:52-62.**

Duffy antigen receptor for chemokines (DARC) expressed on red blood cells influences plasma levels of HIV-1-suppressive and proinflammatory chemokines such as CCL5/RANTES. DARC is also the red blood cell receptor for Plasmodium vivax. Africans with DARC\_46C/C genotype, which confers a DARC negative phenotype, are resistant to vivax malaria. Here, Weijing and co-authors show that HIV-1 attaches to red blood cells via DARC, effecting trans-infection of target cells. In African Americans, DARC\_46C/C is associated with 40% increase in the odds of acquiring HIV-1. If extrapolated to Africans, approximately 11% of the HIV-1 burden in Africa may be linked to this genotype. After infection occurs, however, DARC-negative red blood cell status is associated with slower disease progression. Furthermore, the disease-accelerating effect of a previously described CCL5 polymorphism is evident only in DARC-expressing and not in DARC-negative HIV-infected individuals. Thus, DARC influences HIV susceptibility by mediating trans-infection of HIV-1 and by affecting both chemokine-HIV interactions and chemokine-driven inflammation. **Editors' note: A genetic trait found in 60 per cent of African-Americans and 90% of Africans increases the risk of HIV infection but decreases the rate of disease progression once infected. The precise mechanisms by which lack of the Duffy antigen receptor for chemokines (DARC) can have this paradoxical effect are now the subject of much theorizing. Although an estimated 11% of the HIV epidemic in sub-Saharan Africa may be accounted for by people being DARC-negative, this does not change our basic understanding of the structural and behavioural determinants that lead people to being exposed to HIV in the first place.**

Waters L, Mandalia S, Randell P, Wildfire A, Gazzard B, Moyle G. The impact of HIV tropism on decreases in CD4 cell count, clinical progression, and subsequent response to a first antiretroviral therapy regimen. *Clin Infect Dis*. 2008;46(10):1617-23.

Human immunodeficiency virus (HIV) uses 2 distinct chemokine receptors, CCR5 (R5) or CXCR4 (X4), during entry. Viruses may be R5 tropic, X4 tropic, or dual/mixed tropic. R5-tropic virus predominates at high CD4 cell counts, with the number of X4-tropic strains increasing as CD4 cell count decreases. Waters and colleagues investigated the relationship between tropism and decreases in CD4 cell count before antiretroviral therapy initiation, the frequency of clinical events, and responses to antiretroviral therapy in a cohort of treatment-naive patients. Four hundred two treatment-naive patients underwent tropism determination; 326 harboured R5-tropic virus, and 76 harboured X4- or dual/mixed-tropic virus. After adjustment for baseline characteristics, the rate of decrease in CD4 cell count was significantly greater in patients infected with X4- or dual/mixed-tropic virus at 12 months (P=.026). Two hundred twenty-nine individuals infected with R5-tropic virus and 60 individuals infected with X4- or dual/mixed-tropic virus commenced antiretroviral therapy between tropism testing and the time of data analysis. Time to viral suppression and the proportion of patients achieving viral suppression were similar at 6, 12, and 24 months. CD4 cell count increases were similar. Clinical events were significantly more common in the group infected with X4- or dual/mixed-tropic virus. Multivariate analysis demonstrated a relative risk of experiencing a clinical event of 2.56 (95% confidence interval, 1.37-4.76; P=.003) among patients infected with X4- or dual/mixed-tropic virus. The authors conclude that the presence of dual/mixed- or X4-tropic virus has a deleterious effect on CD4 cell count decrease and risk of clinical disease. Response to standard antiretroviral therapy is not

affected by viral tropism. **Editors' note: Tropism is a word derived from the Greek meaning to turn. Most tropism is towards the source of the stimulus. In the case of HIV, when viral gp120 binds to CD4 cells, a chemokine receptor site on the cell becomes exposed. R5-tropic viruses will then use the CCR5 chemokine receptor on the cell surface, X4-tropic viruses will use the CXCR4 receptor and yet other viruses are dual tropic, using either receptor. It is unclear why X4-tropic strains increase as CD4 cell counts decrease but they are associated with increased clinical progression. At some point in the future, tropism testing may help determine when to start antiretroviral treatment.**

## **2. HIV Testing**

Sebert Kuhlmann AK, Kraft JM, Galavotti C, Creek TL, Mooki M, Ntuny R. Radio role models for the prevention of mother-to-child transmission of HIV and HIV testing among pregnant women in Botswana. *Health Promot Int.* 2008 Apr 11 [Epub ahead of print]

Although Botswana supports a program for the prevention of mother-to-child-transmission of HIV (PMTCT), many women initially did not take advantage of the program. Using data from a 2003 survey of 504 pregnant and post-partum women, Sebert Kuhlmann and his colleagues assessed associations between exposure to a long-running radio serial drama that encourages use of the PMTCT program and HIV testing during pregnancy. Controlling for demographic, pregnancy and other variables, women who spontaneously named a PMTCT character in the serial drama as their favourite character were nearly twice as likely to test for HIV during pregnancy as those who did not. Additionally, multiparity, knowing a pregnant woman taking AZT, having a partner who tested, higher education and PMTCT knowledge were associated with HIV testing during pregnancy. Identification with characters in the radio serial drama is associated with testing during pregnancy. Coupled with other supporting elements, serial dramas could contribute to HIV prevention, treatment and care initiatives. **Editors' note: This programme went further than public service announcements and counselling sessions to raise awareness of PMTCT services. It used two fundamental principles: modelling (showing people how to change) and reinforcement (supporting their efforts to change and to maintain healthy behaviours). The radio drama was the modelling component and may have helped some women to see HIV testing in pregnancy as a good choice supported by social norms. It is interesting to speculate whether this programme paved the way for broad acceptance of the introduction of a routine offer of antenatal testing in 2004.**

Wringe A, Isingo R, Urassa M, Maiseli G, Manyalla R, Chagalucha J, Mngara J, Kalluvya S, Zaba B. Uptake of HIV voluntary counselling and testing services in rural Tanzania: implications for effective HIV prevention and equitable access to treatment. *Trop Med Int Health.* 2008;13(3):319-27.

Wringe and colleagues aimed to describe the associations between socio-demographic, behavioural and clinical characteristics and the use of HIV voluntary counselling and testing (VCT) services among residents in a rural ward in Tanzania. Eight thousand nine hundred and seventy participants from a community-based cohort were interviewed, provided blood for research HIV testing, and were offered VCT. Univariate and multivariate logistic regression was used to identify socio-demographic, clinical, and behavioural factors associated with VCT use. Although 31% (1246/3980) of men and 24% (1195/4990) of women expressed an interest in the service, only 12% of men and 7% of women subsequently completed VCT.

Socio-demographic factors, such as marital status, area of residence, religion and ethnicity influenced VCT completion among males and females in different ways, while self-perceived risk of HIV, prior knowledge of VCT, and sex with a high-risk partner emerged as important predictors of VCT completion among both sexes. Among males only, those infected with HIV for 5 years or less tended to self-select for VCT compared to HIV-negatives (adjusted odds ratio = 1.43; 95% CI: 0.99-2.14). This contributed to a higher proportion of HIV-positive males knowing their status compared to HIV-positive females. In this setting, a disproportionate number of HIV-positive women are failing to learn their status, which has implications for equitable access to onward referral for care and treatment services. Evidence that some high-risk behaviours may prompt VCT use is encouraging, although further interventions are required to improve knowledge about HIV risk and the benefits of VCT. Targeted interventions are also needed to promote VCT uptake among married women and rural residents. **Editors' note: Both the proportion of people interested in learning their HIV serostatus and the proportion of people who actually got tested are very low for a country with a sizeable HIV epidemic. It is likely that fear of stigma and discrimination had remained an important barrier to HIV testing during this study, since the Tanzanian government had already announced on radio and in newspapers that it intended to start providing free antiretroviral treatment through major hospitals.**

### **3. Sexual transmission**

Grijzen ML, Graham SM, Mwangome M, Githua P, Mutimba S, Wamuyu L, Okuku HS, Price MA, McClelland SR, Smith AD, Sanders EJ. Screening for genital and anorectal sexually transmitted infections in HIV prevention trials in Africa. *Sex Transm Infect.* 2008 Mar 28 [Epub ahead of print]

Grijzen and co-authors' objectives were (1) to demonstrate the value of routine, basic sexually transmitted infections screening at enrolment into an HIV-1 vaccine feasibility cohort study; and (2) to highlight the importance of soliciting a history of receptive anal intercourse in adults identified as being at higher risk for HIV exposure. Routine sexually transmitted infections screening was offered to adults at higher risk for HIV-1 upon enrolment into a cohort study in preparation for HIV-1 vaccine trials. Risk behaviours and sexually transmitted infections prevalence were summarized, and the value of microscopy assessed. Associations between prevalent HIV-1 infection and receptive anal intercourse or prevalent sexually transmitted infections were evaluated with multiple logistic regression. Participants had a high burden of untreated sexually transmitted infections. Symptom-directed management would have missed 67% of urethritis cases in men and 59% of cervicitis cases in women. Receptive anal intercourse was reported by 36% of male and 18% of female participants. Receptive anal intercourse was strongly associated with HIV-1 in men (adjusted odds ratio [aOR] = 3.8, 95% CI 2.0-6.9), and independently associated with syphilis in women (aOR 12.9, 95% CI 3.4-48.7). Grijzen and colleagues conclude that high-risk adults recruited for HIV-1 prevention trials carry a high sexually transmitted infections burden. Symptom-directed treatment may miss many cases, and simple laboratory-based screening can be done with little cost. Risk assessment should include questions about anal intercourse and whether condoms were used. Sexually transmitted infections screening, including specific assessment for anorectal disease, should be offered in African research settings recruiting participants at high risk for HIV-1 acquisition. **Editors' note: This article is about the importance of screening potential vaccine trial participants for sexually transmitted infections. But it is also about unprotected receptive anal**

intercourse, considered to be the most efficient mode of sexual transmission of HIV, whether among men who have sex with men or heterosexual couples. If questions that are carefully worded are not asked, no answers will be given and the opportunity for intensified risk reduction counselling will be missed.

#### 4. *Antiretroviral treatment*

The ART-LINC Collaboration of the International Databases to Evaluate AIDS (IeDEA). Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America. *Trop Med Int Health*. 2008;13(7):870-9

The collaboration set out to describe temporal trends in baseline clinical characteristics, initial treatment regimens, and monitoring of patients starting antiretroviral therapy in resource-limited settings. The collaborators analysed data from 17 antiretroviral therapy programmes in 12 countries in sub-Saharan Africa, South America and Asia. Patients aged 16 years or older with documented date of start of highly active antiretroviral therapy were included. Data were analysed by calculating medians, interquartile ranges and percentages by regions and time periods. Not all centres provided data for 2006 and therefore 2005 and 2006 were combined. A total of 36 715 patients who started antiretroviral therapy 1996-2006 were included in the analysis. Patient numbers increased substantially in sub-Saharan Africa and Asia, and the number of initial regimens declined, to four and five, respectively, in 2005-2006. In South America 20 regimes were used in 2005-2006. A combination of 3TC/D4T/NVP was used for 56% of African patients and 42% of Asian patients; AZT/3TC/EFV was used in 33% of patients in South America. The median baseline CD4 count increased in recent years, to 122 cells/mul (interquartile range 53-194) in 2005-2006 in Africa, 134 cells/mul (interquartile range 72-191) in Asia, and 197 cells/mul (interquartile range 61-277) in South America, but 77%, 78% and 51%, respectively, started with <200 cells/mul in 2005-2006. In all regions baseline CD4 cell counts were higher in women than men: differences were 22cells/mul in Africa, 65 cells/mul in Asia and 10 cells/mul in South America. In 2005-2006 a viral load at 6 months was available in 21% of patients Africa, 8% of Asian patients and 73% of patients in South America. Corresponding figures for 6-month CD4 cell counts were 74%, 77% and 81%. The public health approach to providing ART proposed by the World Health Organization has been implemented in sub-Saharan Africa and Asia. Although CD4 cell counts at the start of ART have increased in recent years, most patients continue to start with counts well below the recommended threshold. Particular attention should be paid to more timely initiation of ART in HIV-infected men. **Editors' note: This database of HIV-infected patients followed clinically in resource-limited settings permits valuable analyses of trends over time in the scale-up of the public health approach to antiretroviral treatment. Standardised first-line and second-line regimens, simplified decision making, and standardised clinical and laboratory monitoring are key features of this approach. Although patients in South America are starting on treatment with less severe immunodeficiency, the majority of African and Asian patients are starting late, which has important implications both for early mortality and for more rapid disease progression.**

Hallett TB, Gregson S, Dube S, Garnett GP. The Impact of Monitoring HIV Patients Prior to Treatment in Resource-Poor Settings: Insights from Mathematical Modelling. *PLoS Med*. 2008;5(3):e53

The roll-out of antiretroviral treatment in developing countries concentrates on finding patients currently in need, but over time many HIV-infected individuals will be identified who will require treatment in the future. Hallett and colleagues investigated the potential influence of alternative patient management and antiretroviral treatment initiation strategies on the impact of antiretroviral treatment programmes in sub-Saharan Africa. They developed a stochastic mathematical model representing disease progression, diagnosis, clinical monitoring, and survival in a cohort of 1,000 hypothetical HIV-infected individuals in Africa. If individuals primarily enter antiretroviral treatment programmes when symptomatic, the model predicts that only 25% will start treatment and, on average, 6 life-years will be saved per person treated. If individuals are recruited to programmes while still healthy and are frequently monitored, and CD4(+) cell counts are used to help decide when to initiate antiretroviral treatment, three times as many are expected to be treated, and average life-years saved among those treated increases to 15. The impact of programmes can be improved further by performing a second CD4(+) cell count when the initial value is close to the threshold for starting treatment, maintaining high patient follow-up rates, and prioritising monitoring the oldest (>= 35 y) and most immune-suppressed patients (CD4(+) cell count <= 350). Initiating antiretroviral treatment at higher CD4(+) cell counts than the World Health Organization recommends leads to more life-years saved, but disproportionately more years spent on antiretroviral treatment. The authors conclude that the overall impact of antiretroviral treatment programmes will be limited if rates of diagnosis are low and individuals enter care too late. Frequently monitoring individuals at all stages of HIV infection and using CD4 cell count information to determine when to start treatment can maximise the impact of ART. **Editors' note: This modelling work demonstrates that measuring CD4 cells frequently will save more life-years because it can trigger the start of antiretroviral treatment before the immune system is irreversibly damaged. In resource-limited settings, more life years can be saved per year on antiretroviral treatment by frequent CD4 cell count measurements. Therefore, there are strong arguments in favour of improved patient monitoring even before treatment initiation.**

### **5. Post-exposure prophylaxis**

Loutfy MR, Macdonald S, Myhr T, Husson H, Du Mont J, Balla S, Antoniou T, Rachlis A. Prospective cohort study of HIV post-exposure prophylaxis for sexual assault survivors. *Antivir Ther.* 2008;13(1):87-95

There is a lack of standardized programs for HIV counselling and post-exposure prophylaxis (PEP) in the setting of sexual assault. Loutfy and associates conducted an 18-month prospective cohort study assessing universal HIV counselling for all sexual assault survivors presenting to 18 Ontario Sexual Assault Treatment Centres. HIV PEP was universally offered to those at risk of HIV infection (high risk or unknown risk) presenting < or =72 h after the assault, using Combivir (Lamivudine/Zidovudine) one pill and Kaletra (Lopinavir/Ritonavir) three capsules twice a day for 28 days. Those who accepted HIV PEP were monitored via a schedule of frequent follow ups. The primary outcomes were acceptance and completion rates, and their predictors were determined using multivariable logistic regression. Adverse events were categorized using a standardized toxicity grading system. Of the 900 evaluable participants eligible for PEP, 798 (69 at high risk and 729 at unknown risk) were offered treatment. Acceptance rates were 66.7% (n=46) and 41.3% (n=301) for participants at high risk and unknown risk, respectively. Participants at high risk were 2.2 times more likely to

accept PEP than those at unknown risk (adjusted odds ratio 2.2; 95% confidence interval 1.2-4.0; P=0.01). Overall, 23.9% high-risk (n=11) and 33.2% unknown-risk participants (n=100) completed PEP (P=0.20). Predictors of acceptance and completion included assault by a stranger and participant anxiety. Adverse events were common, with 77.1% of participants reporting grade 2-4 symptoms. A province-wide standardized program of universal HIV counselling and offering of PEP to sexual assault survivors with frequent follow up was successfully implemented and feasible. **Editors' note: Post-exposure prophylaxis for sexual assault survivors requires contact with the health system within 72 hours of the attack, availability of antiretroviral drugs and willingness to take them, and, in most cases, consent for HIV testing and counselling. Both anxiety and perceived risk that the assailant could have been HIV-positive influence uptake and completion, but so do side effects. Only 32% of those who started on post-exposure prophylaxis actually finished the 28-day course.**

## **6. Trial Design and Conduct**

Morin SF, Morfit S, Maiorana A, Aramrattana A, Goicochea P, Mutsambi JM, Robbins JL, Richards TA. Building community partnerships: case studies of Community Advisory Boards at research sites in Peru, Zimbabwe, and Thailand. Clin Trials. 2008;5(2):147-56.

Differences in resources, knowledge, and infrastructure between countries initiating and countries hosting HIV prevention research trials frequently yield ethical dilemmas. Community Advisory Boards have emerged as one strategy for establishing partnerships between researchers and host communities to promote community consultation in socially sensitive research. Morin and co-authors undertook to understand the evolution of Community Advisory Boards and community partnerships at international research sites conducting HIV prevention trials. Three research sites of the HIV Prevention Trials Network (HPTN) were selected to include geographical representation and diverse populations at risk for HIV exposure - Lima, Peru; Chitungwiza, Zimbabwe; and Chiang Mai, Thailand. Data collection included review of secondary data, including academic publications and site-specific progress reports; observations at the research sites; face-to-face interviews with Community Advisory Boards members, research staff, and other key informants; and focus groups with study participants. Rapid assessment techniques were used for data analysis. The authors found that two of the three Community Advisory Boards developed new strategies for community representation in response to new studies. All three Community Advisory Boards expanded their original function and became advocates for broader community interests beyond HIV prevention. The participation and input of community representatives, in response to critical incidents that occurred at the sites over the past five years, helped to solidify partnerships between researchers and communities. In terms of limitations the authors point out that Rapid Assessment is an exploratory methodology designed to provide an understanding of a situation based on the integration of multiple data sources, collected within a short period of time, without a formal examination of transcribed and coded data. Case studies, as a method, are meant to draw out what can be learned from a single case but are not, in the scientific sense, generalizable. They conclude that in developing countries, Community Advisory Boards can be dynamic entities that enhance the HIV research process, assist in responding to issues involving research ethics, and prepare communities for HIV research. **Editors' note: This assessment of changes in community advisory board conduct and roles over a five year period found that at each site a conflict or challenge arose in which the views and assistance of community**

advisory board members became not only valuable to the research team but also important for the future success of the research. These conflicts or challenges generated substantial interactions of mutual benefit as issues were debated which led to a more genuine partnership. Community advisory boards clearly can be dynamic entities striving to better represent and advocate for the communities.

Djomand G, Metch B, Zorrilla CD, Donastorg Y, Casapia M, Villafana T, Pape J, Figueroa P, Hansen M, Buchbinder S, Beyrer C; for the 903 Protocol Team. The HVTN Protocol 903 Vaccine Preparedness Study: Lessons Learned in Preparation for HIV Vaccine Efficacy Trials. *J Acquir Immune Defic Syndr*. 2008;48(1):82-9 2008

Successful recruitment and retention of HIV-uninfected at-risk participants are essential for HIV vaccine efficacy trials. A multicountry vaccine preparedness study was started in 2003 to assess enrolment and retention of HIV-negative high-risk participants, and to assess their willingness to participate in future vaccine efficacy trials. HIV-negative high-risk adults were recruited in the Caribbean, in Southern Africa, and in Latin America, and were followed for 1 year. Participants included men who have sex with men, heterosexual men and women, and female sex workers. History of sexually transmitted infections and sexual risk behaviours were recorded with HIV testing at 0, 6, and 12 months, and willingness to participate in future vaccine trials was recorded at 0 and 12 months. Recruitment, retention, and willingness to participate in future trials were excellent at 3 of the 6 sites, with consistent declines in risk behaviours across cohorts over time. Although not powered to measure seroincidence, HIV seroincidence rates per 100 person-years (95% confidence interval [CI]) were as follows: 2.3 (95% CI: 0.3 to 8.2) in Botswana, 0.5 (95% CI: 0 to 2.9) in the Dominican Republic, and 3.1 (95% CI: 1.1 to 6.8) in Peru. The HIV Vaccine Trials Network 903 study helped to develop clinical trial site capacity, with a focus on recruitment and retention of high-risk women in the Americas, and improved network and site expertise about large-scale HIV vaccine efficacy trials. **Editors' note: Finding populations with sufficient risk for HIV infection to support the seroincidence demands of trials is a start but they must also have high rates of retention for there to be adequate power to confirm or refute the study's hypothesis. Even participating in a study to assess enrolment, retention, and HIV incidence can lead to declines in risk behaviour and HIV incidence, above those already happening in the overall general population. Such a positive effect of being studied is sometimes called the Hawthorne Effect.**

Hughes S, L Cuffe R, Lieftucht A, Garrett Nichols W. Informing the selection of futility stopping thresholds: case study from a late-phase clinical trial. *Pharm Stat*. 2008 Mar 27 [Epub ahead of print]

In an environment where (i) potential risks to subjects participating in clinical studies need to be managed carefully, (ii) trial costs are increasing, and (iii) there are limited research resources available, it is necessary to prioritize research projects and sometimes re-prioritize if early indications suggest that a trial has low probability of success. Futility designs allow this reprioritization to take place. This paper reviews a number of possible futility methods available and presents a case study from a late-phase study of an HIV therapeutic, which utilized conditional power-based stopping thresholds. The two most challenging aspects of incorporating a futility interim analysis into a trial design are the selection of optimal stopping thresholds and the timing of the analysis, both of which require the balancing of various risks. The paper outlines a number of graphical aids that proved

useful in explaining the statistical risks involved to the study team. Further, the paper outlines a decision analysis undertaken which combined expectations of drug performance with conditional power calculations in order to produce probabilities of different interim and final outcomes, and which ultimately led to the selection of the final stopping thresholds.

**Editors' note: Early indications that a trial has low probability of success - with success defined as confirming or refuting the trial hypothesis - can lead to the stopping of a trial for futility. Although this saves resources, stopping a trial prior to its conclusion because its key endpoints will not be met makes it impossible to determine whether results for secondary endpoints would have generated useful hypotheses for future investigation. It is important to decide up front what the stopping rules will be with respect to all endpoints and understand the consequences and anticipate them.**

## **7. Cardiovascular disease and HIV**

Circulation. 2008 Jul 8;118(2):e29-35. Epub 2008 Jun 19. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Currier JS, Lundgren JD, Carr A, Klein D, Sabin CA, Sax PE, Schouten JT, Smieja M; Working Group 2.

In the mid-1990s, case reports of myocardial infarction in young patients infected with human immunodeficiency virus (HIV) sparked interest in the relationship between HIV infection and cardiovascular disease. Although the initial focus was primarily on the relationship between dyslipidemia associated with antiretroviral therapy and cardiovascular risk, a broader appreciation of the complex interplay between traditional risk factors for cardiovascular disease and HIV infection has emerged more recently. Several groups of investigators have designed studies to examine various aspects of the relationship between HIV infection, traditional cardiovascular risk factors, antiretroviral therapy, and short- and longer-term cardiovascular risk. Studies have included both clinical end points (myocardial infarction, hospitalization for myocardial infarction or angina, and revascularization) and surrogate markers of atherosclerosis (endothelial function or carotid intima-media thickness). Successive studies have generally improved in quality, with inclusion of data on traditional risk factors, longer follow-up, and more diverse patient populations. HIV and antiretroviral therapy can contribute to an altered risk of cardiovascular disease in 3 principal ways: (1) HIV may serve as a marker to identify a subgroup of the general population with an altered prevalence of traditional cardiovascular risk factors, unrelated to HIV or antiretroviral therapy (e.g., HIV-infected patients may have higher smoking rates); (2) HIV or antiretroviral therapy may affect the risk of developing a traditional cardiovascular risk factor (e.g., HIV or antiretroviral therapy may worsen dyslipidemia); and (3) HIV or antiretroviral therapy may affect the pathogenetic process that leads to cardiovascular disease in ways other than via an effect on traditional risk factors (e.g., through effects on inflammation or endothelial function). Importantly, there is substantial evidence to suggest that all 3 mechanisms are in operation and affect the risk of cardiovascular disease in patients infected with HIV. All 3 factors should be considered in epidemiological studies assessing the relationship between cardiovascular disease and HIV disease. **Editors' note: Many factors can influence cardiovascular risk in people living with HIV. Some increase risks (e.g. lipid problems, insulin resistance, smoking, increasing age) while others decrease risk (antiretroviral treatment reducing inflammation and improving endothelial function). This review provides a helpful framework for**

## understanding cardiovascular risk in relation to HIV infection and determining future research priorities.

Giuliano ID, de Freitas SF, de Souza M, Caramelli B. Subclinic atherosclerosis and cardiovascular risk factors in HIV-infected children: PERI study. *Coron Artery Dis*. 2008 May;19(3):167-172.

Giuliano and colleagues aimed to compare carotid intima-media thickness of children and adolescents with and without HIV infection and determine associations among independent socio-demographic, clinical or cardiovascular variables and carotid intima-media thickness in HIV-infected children and adolescents. This was a matched case-control study comparing 83 HIV-infected and 83 healthy children and adolescents. Clinical and laboratorial parameters, carotid intima-media thickness, and echocardiogram were measured. They found the carotid intima-media thickness was higher in HIV-infected individuals (median 480 µm; interquartile range 463-518 µm) compared with controls (426 µm; range 415-453 µm,  $P < 0.001$ ). In addition, the HIV-infected group showed higher levels of high-sensitive C-reactive protein (medians 1.0 mg/l vs. 0.4 mg/l,  $P < 0.001$ ), glycated hemoglobin (6.1+/-0.9 vs. 5.7+/-0.8%,  $P = 0.028$ ) and triglycerides (medians 0.9 vs. 0.8 mmol/l,  $P = 0.031$ ). Finally, this group showed lower levels of total and high-density lipoprotein-cholesterol. After multivariate analysis, increased carotid intima-media thickness was positively associated with stavudine use [odds ratio (OR): 18.9,  $P = 0.005$ ], left atrial/aorta index (OR: 15.6,  $P = 0.019$ ), suprailiac skinfold (OR: 7.9,  $P = 0.019$ ), tachypnea (OR: 5.9,  $P = 0.031$ ), CD8 lymphocyte count (OR: 5.7,  $P = 0.033$ ) and CD4 T-lymphocyte count (OR: 5.5,  $P = 0.025$ ). Carotid intima-media thickness increment was negatively associated with total cholesterol (OR: 0.2,  $P = 0.025$ ) and with CD8 zenith (OR: 0.1,  $P = 0.007$ ). In this sample of children and adolescents, having HIV infection was associated with increased carotid intima-media thickness and elevated prevalence of cardiovascular risk factors. These findings suggest that this group should be included in cardiovascular prevention programs. **Editors' note: In this Brazilian study, cases and controls were matched for age, sex, and economic class. Despite significantly higher intake of calories, lipids, and saturated fatty acids in the control group, the children and adolescents with HIV infection had worse metabolic and vascular parameters. These are likely multi-factorial in origin and the possibility that poor nutrition, physical inactivity, and chronic inflammatory stress are playing roles cannot be excluded.**

### 8. *Molecular Epidemiology*

Sarker MS, Rahman M, Yirrell D, Campbell E, Rahman AS, Islam LN, Azim T. Molecular evidence for polyphyletic origin of human immunodeficiency virus type 1 subtype C in Bangladesh. *Virus Res*. 2008;135(1):89-94

HIV-1 positive blood samples were collected between 1999 and 2005 from population groups most at risk of HIV infection in Bangladesh through the national surveillance, from clients of the Voluntary Counselling and Testing (VCT) Unit for HIV at the International Centre for Diarrhoeal Diseases Research, Bangladesh, and a from survey of HIV in patients with tuberculosis. Partial sequences of the gag gene were used for subtyping the HIV strains by nested polymerase chain reaction using selective primers. Of the 198 HIV strains tested, subtype C (41.4%) was the commonest strain identified. Phylogenetic analysis of Bangladeshi subtype C strains showed that they clustered in polyphyletic branches representing HIV strains from different parts of the world. Most of the strains from injecting drug users clustered together and were similar to Indian strains. The VCT strains however were very

heterogeneous and clustered with strains from India, Myanmar, Ethiopia and Zimbabwe. Data suggest that there have been few introductions into the injecting drug user population where the epidemic is driven by indigenous transmission. On the other hand there have been many and regular introductions of subtype C viruses through migrant workers in the VCT group. Very little overlap was observed in the strains obtained from injecting drug users and those from other population groups. **Editors' note: Injecting drug use transmission of subtype C virus in Bangladesh appears to be confined primarily to the community of people who inject drugs, with the strains being very similar. The majority of strains from the VCT clients were not subtype C and those that were subtype C were a very heterogeneous population, suggesting transmission from a variety of different geographical sources. None of the strains from the VCT clients clustered with isolates from the injecting drug users, suggesting little interaction between these two populations that could lead to HIV transmission. Studying HIV subtypes can provide a window on the dynamics of a country's epidemic.**

## **9. Spirituality**

Nilmanat K, Street AF. Karmic quest: Thai family caregivers promoting a peaceful death for people with AIDS. *Contemp Nurse*. 2007;27(2):94-103.

Nilmanat and colleagues report the constructions of karma by four Thai family caregivers living with a dying person with AIDS in southern Thailand. These four families form a subset of a larger ethnographic case study exploring the experiences of families living with a relative with AIDS. Serial interviews, observations, and field journals were used as data collection methods with the four families. The findings indicated that the karmic quest is a dominant theme in the narratives of these families caring for their loved ones dying with AIDS. The 'calm and peaceful' death that is described in the palliative care literature equated with their desire for the Buddhist philosophy of a harmonious death. The families used the law of karma and reincarnation as their main frame of reference and mobilised their religious resources to create meaning and purpose. Karmic healing activities were aimed at ending suffering, promoting a peaceful and calm death and ensuring a better life in the next one. The findings are important for the development of palliative nursing practice in Thailand by acknowledging religious and cultural values to promote peaceful death.

**Editors' note: Palliative care aims to provide the best quality of life and relieve the suffering of people living with an incurable illness while offering comfort and support to their families and carers. It is a holistic approach which takes account of emotional, psychological, and spiritual needs as well as physical ones. In southern Thailand, Buddhist philosophy and karmic healing activities provide just such a holistic approach.**

Ridge D, Williams I, Anderson J, Elford J. Like a prayer: the role of spirituality and religion for people living with HIV in the UK. *Sociol Health Illn*. 2008;30(3):413-28.

Over 40,000 people are now living with diagnosed HIV in the United Kingdom (UK). There is, however, uncertainty about how people with HIV use religion or spirituality to cope with their infection. Adopting a modified grounded theory approach, Ridge and colleagues analysed individual and group interviews with the people most affected by HIV in the UK: black African heterosexual men and women and gay men (mostly white). For the majority of black African heterosexual men and women in our study, religion was extremely important. The authors found that gay men in the study were less religious than black Africans, although many were spiritual in some way. Black African individuals constructed their spiritual

narratives as largely Christian or collective, while gay men described more individualistic or 'New Age' approaches. The authors developed a six-level heuristic device to examine the ways in which prayer and meditation were deployed in narratives to modulate subjective wellbeing. These were: (i) creating a dialogue with an absent counsellor; (ii) constructing a compassionate 'life scheme'; (iii) interrupting rumination; (iv) establishing mindfulness; (v) promoting positive thinking, and (vi) getting results. That people with HIV report specific subjective benefits from prayer or meditation presents a challenge to secular healthcare professionals and sociologists. **Editors' note: Open-ended in-depth interviews and focus groups revealed that most black Africans in this study were deeply spiritual in their approach to living with HIV and despite high stigma levels in their place of worship they relied heavily on their religion for support. Although some gay men had deep misgivings about religion and its wounding hostility to gay sexuality, they sought meaning in life, were striving to live in harmony and balance, and saw earth as a stepping-stone to another existence. In both groups, whether it was secular, spiritual, or religious in nature, prayer helped interrupt negative rumination and promoted mindfulness.**

### **10. Hepatitis**

Modi AA, Feld JJ. Viral hepatitis and HIV in Africa. *AIDS Rev.* 2007;9(1):25-39.

With increasing access to antiretroviral therapy across sub-Saharan Africa, progress is finally being made in combating the devastating HIV epidemic. As HIV-infected individuals live longer, the effects of co-infection with chronic hepatitis B and C will likely become an increasingly relevant issue. Indeed, HIV adversely affects the natural history of hepatitis B and hepatitis C, both of which are endemic across the African continent. Issues ranging from appropriate diagnostic testing to prevention and treatment are affected by HIV coinfection, particularly in resource-limited settings. In addition, some of the more complex problems such as occult infection, immune reconstitution, and antiretroviral hepatotoxicity are becoming increasingly important considerations. In this review, Modi and Feld present the available data on co-infection in Africa with a major emphasis on prevalence, routes of transmission, prevention, and treatment strategies. **Editors' note: This review reveals surprising information: 70-75% of people across Africa are protected from sexual acquisition of hepatitis B because they were infected during labour and delivery or in early life but 50 million people are chronic carriers. Africa has the highest prevalence of hepatitis C with 5.3% of the population infected. A history of exposure to medical injections or dental therapy is a significant risk factor. Both HIV/hepatitis B co-infection and HIV/hepatitis C co-infection are not uncommon and have implications for prevention and clinical management, particularly as people are living longer with the introduction of antiretroviral treatment.**

### **11. Young people**

Bastien S, Sango W, Mnyika KS, Masatu MC, Klepp KI. Changes in exposure to information, communication and knowledge about AIDS among school children in Northern Tanzania, 1992-2005. *AIDS Care.* 2008;20(3):382-7.

Bastien and colleagues investigate changes in primary school students' reported exposure to AIDS information and communication, and knowledge levels from 1992 to 2005. A repeated cross-sectional design was used. In 1992, a self-administered questionnaire was completed by 2,026 sixth and seventh grade students from 18 randomly selected primary schools in Arusha and Kilimanjaro regions, Tanzania. The same procedures were repeated in 2005 with a

sample of 2,069 students. Mean values with 95% confidence intervals are reported. Chi-square was used to test for differences in proportions. Students in 2005 reported higher levels of exposure to information and communication from all sources than in 1992. Knowledge scores also increased, yet there was a significant decline in four variables, two of which are related to transmission and two of which are factual. An alarming decline in awareness of the condom as a preventative measure was found. Findings also indicate that myths related to transmission and infection persist. Salient sex differences remain, but the knowledge gap is narrowing. Interventions should aim to stimulate discussion in young people's social networks in order to increase overall exposure to AIDS information, communication and knowledge. **Editors' note: This large study of primary school students, drawn from the same location as a similar study conducted 13 years before, showed little improvement. Its findings underscore the continuing importance of sustained efforts to improve young people's communication skills and provide them with opportunities to discuss HIV-related issues, challenge misconceptions, and address recurring myths. Examples include negative public discourse about condom efficacy and use and persistent myths about HIV acquisition via mosquito bites.**

## **12. Malaria**

Brahmbhatt H, Sullivan D, Kigozi G, Askin F, Wabwire-Mangenm F, Serwadda D, Sewankambo N, Wawer M, Gray R. Association of HIV and Malaria With Mother-to-Child Transmission, Birth Outcomes, and Child Mortality. *J Acquir Immune Defic Syndr*. 2008;47(4):472-476.

Brahmbhatt and colleagues set out to assess the impact of HIV and malaria coinfection on mother-to-child HIV transmission (MTCT) and adverse birth outcomes. One hundred nine HIV-positive mother-infant pairs with a malaria diagnosis were identified in a community cohort and followed up postpartum. Maternal malaria was diagnosed by a rapid immunochromatographic test on sera and histopathologic examination of placenta. Infant HIV was diagnosed within 6 weeks of birth using polymerase chain reaction (PCR) to capture in-utero and intrapartum HIV transmission. Log binomial models were used to assess the relative risk of MTCT, low birth weight, and preterm birth associated with malaria. Approximately 17.4% of infants were HIV positive at or around birth, and the prevalence of serologic and placental malaria were 31% and 32%, respectively. HIV-positive mothers with serological immunochromatographic test malaria were significantly more likely to have low-birth-weight infants, and low-birth-weight infants had significantly higher risk of MTCT compared with infants of normal birth weight. Although placental and serologic immunochromatographic test malaria were significantly associated with MTCT, after adjusting for maternal HIV viral load, the risk of MTCT was significantly increased only for mothers coinfecting with placental malaria (relative risk [RR] = 7.9, P = 0.025). The authors conclude that placental malaria increases the risk of MTCT after adjustment for viral load. Programmes should focus on enhanced malaria prevention during pregnancy to decrease the risk of adverse birth outcomes and MTCT. **Editors' note: Coinfection with malaria and HIV during pregnancy is known to have adverse consequences for morbidity and mortality of infants. Placental malaria is more prevalent in HIV-positive mothers than HIV-negative mothers. In this study using highly sensitive diagnostic methods, placental malaria in pregnant women with HIV infection increased the risk of mother-to-child HIV transmission, irrespective of maternal viral load. This suggests that prevention of placental malaria in pregnancy is important to prevent HIV transmission to infants.**

That was *HIV this week*, signing off.

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